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TITLE: CDK5-A Novel Role in Prostate Cancer Immunotherapy

PRINCIPAL INVESTIGATOR: Dr. Barry Nelkin

CONRTACTING ORGANIZATION: Johns Hopkins University
Baltimore, MD 21287

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Johns Hopkins University
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13. SUPPLEMENTARY NOTES

14. ABSTRACT: Our project will establish the role of CDK5 in promoting the immunosuppressive microenvironment in prostate cancer, and identify optimal strategies for incorporation of CDK5 inhibition to augment the efficacy of immunotherapy for prostate cancer. We will confirm our observation of the involvement of a T cell antitumor response in impaired growth of prostate cancer in immunocompetent murine models of prostate cancer, and characterize the changes induced in immune cells in the tumors. Preclinical translational studies, employing a CDK5 inhibitor in combination with immunotherapies, including immune checkpoint blockers, a prostate cancer vaccine, and other agents will be conducted and optimized in vivo in an immunocompetent prostate cancer model. If successful, these therapeutic strategies can be rapidly advanced to clinical evaluation. In this reporting period, our most significant finding was that depletion of CD4+ and CD8+ T cells resulted in more rapid tumor growth, and significant shortening of survival of mice in the TRAMP prostate cancer model with a prostate specific *Cdk5* gene knockout. The significance of this finding is that it functionally establishes Cdk5 as an important mediator of antitumor immune response in prostate cancer. This opens the potential for a promising therapeutic strategy using a CDK inhibitor to sensitize prostate cancer to immunotherapy.

15. SUBJECT TERMS
Nothing listed

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1. **INTRODUCTION:** Our project will establish the role of CDK5 in promoting the immunosuppressive microenvironment in prostate cancer, and identify optimal strategies for incorporation of CDK5 inhibition to augment the efficacy of immunotherapy for prostate cancer. If successful, these therapeutic strategies can be rapidly advanced to clinical evaluation. Thus, in Specific Aim 1, we will explore mechanisms of immune system activation by Cdk5 deletion in prostate cancer. We will confirm the involvement of a T cell antitumor response in impaired growth of prostate cancer in the TRAMP Cdk5$^{-/-}$ model, by ablating T cells therein. We will then characterize the changes induced in immune cells in the tumors, using FACS and IHC, and in cytokines, using a protein microarray. Functional assays of T cell activation, including proliferation and CTL assays, will be performed. These findings will be extended to other prostate cancer models. In Specific Aim 2, preclinical translational studies, employing a CDK5 inhibitor in combination with immunotherapies, including immune checkpoint blockers, a prostate cancer vaccine, and other agents based on our findings in Specific Aim 1, will be conducted and optimized in vivo in an immunocompetent prostate cancer model, for potential rapid translation to clinical evaluation.

2. **KEYWORDS:** Prostate cancer, CDK5, immunotherapy, vaccine, tumor microenvironment

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

Major Task 1. Involvement of T cell anticancer immune response in impaired growth of TRAMP *Cdk5*$^{-/-}$ model. Months 1-10. Completed, month 10.

Major Task 2. Characterization of antitumor immune response in TRAMP *Cdk5*$^{-/-}$ tumors. Months 1-14. Approximately 70% complete (subtasks 1 and 2 complete)

Major Task 3. Validation of findings in other prostate cancer models. Months 12-24. 15% complete.

Major Task 4: Studies on prostate cancer with ablated *Cdk5* TRAMP-C2 cells with and without *Cdk5* knockdown will be implanted orthotopically in syngeneic mice, and treated with selected immunotherapies. Mice will be monitored for tumor growth and survival. Months 16-30. 10% complete.

Major Task 5: Studies on prostate cancer treated with a pharmacological Cdk inhibitor. TRAMP mice will be treated with a combination of a CDK5 inhibitor and best immunotherapy (from Specific Aim 2, Major Task 4). Mice will be monitored for tumor growth and survival. Dosing sequences will be compared. Months 20-30. Not yet initiated.

Major Task 6: Data will be analyzed, and potential clinical development will be discussed and planned with pharmaceutical company collaborators and liaisons. Months 24-30 and beyond. 5% complete

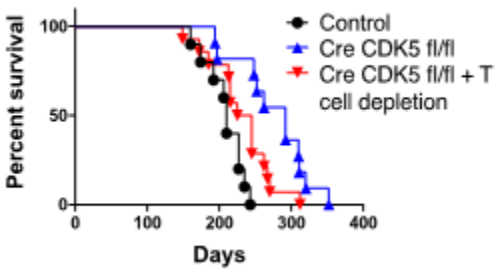
What was accomplished under these goals?

Major activities and specific objectives.

We concentrated on Major Tasks 1 and 2, characterization of the role of Cdk5 in the antitumor immune response in the TRAMP murine model of prostate cancer. In addition, we developed some of the tools (primarily the *Cdk5* knockdown cell lines) for Major Tasks 3 and 4.

Significant results.

Activation of T cell antitumor immunity is a major driver of the increased survival of TRAMP mice mediated by Cdk5 knockout. In our preliminary studies, we had shown that prostate-specific knockout of the *Cdk5* gene in the autochthonous TRAMP model of prostate cancer resulted in impaired tumor growth, and substantially increased lifespan. We further observed that infiltrating CD4+ and CD8+ T cells were significantly increased in the TRAMP tumors with *Cdk5* knockout, and infiltrating CD4+ Tregs were decreased; the CD8+ infiltrating cells were especially enriched for activated cells producing IL-2, TNFα or IFNγ. These observations strongly suggested that *Cdk5* knockout elicited an antitumor immune response that was responsible for some of the impaired tumor growth. In Specific Aim 1 (Major Task1), we tested this hypothesis, by treating TRAMP *Cdk5* knockout mice with a combination of anti-CD4 and anti-CD8 antibodies, to deplete CD4+ and CD8+ T cells. Indeed, this treatment resulted in more rapid tumor growth, and significant shortening of survival of the TRAMP *Cdk5* knockout mice (Fig.1).



Median Survival:

TRAMP + Ctrl Ab = 210

CDK5 Deleted + Ctrl Ab = 292

CDK5 Deleted + αCD4/8 = 235*

*p=0.0252 by Log-rank (Mantel-Cox) test

Figure 1. Survival Benefit of CDK5 Deletion is T Cell Dependent. TRAMP mice with or without Cdk5 conditional deletion were treated with a combination of anti-CD4 (GK1.5) and anti-CD8 (2.43) antibodies, or isotype matched control antibodies,200 mg/mouse, i.p, weekly from age 10 weeks through 18 weeks.

Significance: This finding functionally establishes Cdk5 as an important mediator of antitumor immune response in prostate cancer. This opens the potential for a promising therapeutic strategy using a CDK inhibitor to sensitize prostate cancer to immunotherapy.

Other achievements.

In Major Task 2, we explored the effect of *Cdk5* knockout on cytokine expression in TRAMP tumors. We employed the Proteome Profiler Mouse XL Cytokine Array (R&D Systems). This is a membrane-based ELISA-type antibody array that detects 111 cytokines, including many of the important cytokines involved in immune regulation. We compared cytokine protein levels in tumor lysates from TRAMP wild type and TRAMP *Cdk5* knockout mice (Table 1). A number of immune regulatory cytokines were found to be modulated. Of potential significant interest, IL-33 is increased in the *Cdk5* knockout tumors. IL-33 is a tumor produced cytokine that is an attractant for T cells and NK cells. Using Agilent microarrays, we confirm that IL-33 is increased at the RNA level as well. We are now discussing our next steps in pursuing this finding; these may include treatment of TRAMP *Cdk5* knockout mice to inhibit the putative antitumor immune effect of the *Cdk5* knockout.

	Cytokine Array		
	Mean Signal Difference (≥ 200 arbitrary units)		Fold Change
Higher in Deleted	Lipocalin-2	1470	1.64
	Adiponectin	1325	1.2
	CCL5	1178.1	1.9
	Reg3G	897.5	2.43
	IL-33	633.2	1.42
	EGF	626.7	1.09
	Resistin	507.9	1.74
	ICAM-1	447.3	1.15
	IL-28	444.3	1.58
	IL-27	333.6	1.38
	DPPIV	327.5	1.05
	IL-4	284	1.29

Table 1. Cytokines changed in TRAMP tumors. Spot intensity was quantitated using Image J software. All analytes not meeting a level of change of ≥200 arbitrary units were excluded.

	E-Selectin	275.4	1.75
	LDL-R	254.3	1.42
	Angiopoietin-2	218.7	1.26
	IL-7	201	1.32
Higher in WT	OPN	-725.8	1.55
	C-Reactive Protein/CRP	-534	2.57
	Fetuin A	-296.4	1.09
	VCAM-1	-266.9	1.24
	IGFBP-3	-253.5	1.39
	CCL6	-230.4	1.14
	IL-11	-226.1	1.4
	DLK-1	-206.5	1.24

For Major Tasks 5 and 6, we planned to use either dinaciclib (Merck) or roniciclib (Bayer), multi-CDK inhibitors which were in mid to late stage clinical development. We have active MTAs for both compounds. Unfortunately, both Merck and Bayer have terminated clinical development of these compounds. The compounds are still well suited as "tool compounds," for the preclinical studies in Major Task 5. Nevertheless, to facilitate Major Task 6, we are discussing with other pharmaceutical companies the potential use of their CDK inhibitors in clinical development. We have completed a CDA and discussed with one pharmaceutical company use of their CDK inhibitor, currently in clinical development, and we are submitting an MTA to them. Note that the very impressive CDK4/6 inhibitors, palbociclib (Pfizer) and ribociclib (Novartis), have little or no activity against CDK5, and therefore are unsuitable for the current project.

What opportunities for training and professional development has the project provided?

Nothing to Report.

How were the results disseminated to communities of interest?

Presented seminar to the "Prostate Cancer Amtrak Alliance Summit," an annual meeting of prostate cancer researchers from Baltimore and Philadelphia (May 20, 2016).

Poster presentation at the Eleventh Annual Johns Hopkins Prostate Research Day (October 18, 2016)

Abstract sent September 15, 2016 to Bayer, our corporate supplier of multi-CDK inhibitor roniciclib, for approval for submission for presentation at the AACR 2017 Annual Meeting. Approval to submit granted October 6, 2016. Abstract to be submitted to AACR before November 17, 2016.

What do you plan to do during the next reporting period to accomplish the goals?

Our major focus in the next reporting period will be on the experiments outlined in Major Tasks 3 and 4: 1) confirmation of our findings in a second mouse prostate cancer model (in this case, in the Myc-CaP cell line, with *Cdk5* knockdown using shRNA), and 2) the effect of Cdk5 ablation on sensitivity to a murine therapeutic prostate cancer vaccine. We have successfully knocked down Cdk5 in the Myc-CaP cells, and we have the prostate cancer vaccine (developed by co-PI Dr. Charles Drake), so these experiments should be "ready to go."

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?

The finding, described above, that CDK5 has a role in T cell based antitumor response in prostate cancer is likely to establish CDK5 as a promising immunotherapeutic target in prostate cancer. The impact awaits our wider dissemination of this finding as a manuscript.

What was the impact on other disciplines?

Nothing to Report

What was the impact on technology transfer?

Nothing to Report

What was the impact on society beyond science and technology?

Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them

Anticipated problem (and solution). As discussed above, for Major Tasks 5 and 6, we have been planning to use either dinaciclib (Merck) or roniciclib (Bayer), multi-CDK inhibitors which were in mid to late stage clinical development. We have active MTAs for both compounds. Unfortunately, both Merck and Bayer have terminated clinical development of these compounds. The compounds are still well suited, as "tool compounds," for the preclinical studies in Major Task 5.

Changes that had a significant impact on expenditures

Co-PI Dr. Charles Drake has moved from Johns Hopkins to Columbia University, effective October 1, 2016. This has necessitated a subcontract with Columbia University, and reduction of Dr. Drake's effort to 4%. These changes have been approved by Dr. Ramachandran Arudchandran, Scientific Officer for our project.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to Report

6. PRODUCTS:

Journal publications.

Nothing to Report

Books or other non-periodical, one-time publications.

Nothing to Report

Other publications, conference papers, and presentations.

See above, Accomplishments: How were the results disseminated to communities of interest

Website(s) or other Internet site(s)

Nothing to Report

Technologies or techniques

Nothing to Report

Inventions, patent applications, and/or licenses

Nothing to Report

Other Products

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	*Barry Nelkin, Ph.D.*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*2*
Contribution to Project:	*Dr. Nelkin co-directs all aspects of this project*
Funding Support:	

Name:	*Charles Drake, M.D., Ph.D.*
Project Role:	*Co-PI*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Drake co-directs all aspects of this project*
Funding Support:	

Name:	*Brian Simons, D.V.M., Ph.D.*
Project Role:	*Co-investigator*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*3*

Contribution to Project:	*Dr. Simons performs and interprets the in vitro and in vivo experiments, and participates in supervising the Research Specialist, Ms. Ybanez*
Funding Support:	*Department of Urology startup funds*

Name:	*Maria Ybanez*
Project Role:	*Research Specialist*
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	*11*
Contribution to Project:	*With Dr. Simons, Ms. Ybanez performs the in vitro and in vivo experiments*
Funding Support:	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Nelkin's American Cancer Society Research Project Grant has ended.

What other organizations were involved as partners?

- **Organization Name:** Columbia University Medical School
- **Location of Organization:** New York, NY
- **Partner's contribution to the project:**

  As discussed above, co-PI Dr. Charles Drake has now moved to Columbia University.

OTHER SUPPORT

NELKIN, BARRY D.

ACTIVE

W81XWH-15-1-0670 (PI: Nelkin/Drake)
Title: CDK5-A Novel Role in Prostate Cancer Immunotherapy
Time commitment: 1.92 calendar
Supporting agency: CDMRP
Procuring Contracting/Grants Officer: Kathy Robinson
Address of Grants Officer: 820 Chandler Street, Fort Detrick, MD
Performance period: 09/30/2015-09/29/2018
Level of funding:
Project's Goal(s): The goal of this project is to develop a novel, effective targeted therapeutic strategy for advanced prostate cancer, blocking several of the most common resistance mechanisms to androgen deprivation therapy (ADT), that underlie progression to castration resistant prostate cancer (CRPC)
Specific Aims: 1. Effect of dinaciclib on androgen receptor (AR) S81 phosphorylation and function. **2**. Effect of dinaciclib, alone and in combination with inhibitors of potential compensatory signaling pathways, in human prostate cancer cell lines and xenografts. **3**. Effect of dinaciclib combinations in a model of prostate cancer bone metastasis.
Project Overlap or Parallel: No scientific or budgetary overlap.

SCH727965 (PI: Azad)
Title: LOI 9231: A Phase I Trial of Dinaciclib (SCH727965) and MK2206 in Advanced Solid Tumors with an Expansion Cohort in Advanced Pancreatic Cancer
Time commitment: 0.30 calendar
Supporting agency: Lustgarten Foundation
Procuring Contracting/Grants Officer: Mila McCurrach
Address of Grants Officer: 1111 Stewart Ave, Bethpage, NY 11714
Performance period: 05/01/2013-04/30/2017
Level of funding:
Project's Goal(s): The main project goals are to exhibit that the combination inhibition of downstream effectors of the Ras pathway with MK-2206 and dinaciclib will be tolerable and effective in advanced pancreatic cancer.
Specific Aims: 1. Determine the maximum tolerated dose (MTD), safety, and toxicity of the combination of MK-2206 and dinaciclib in patients with advanced pancreatic adenocarcinoma. **2**. Assess the preliminary efficacy of the combination of MK-2206 and dinaciclib in metastatic pancreatic cancer patients as determined by disease control rate in an expansion cohort of patients at the MTD. **3**. Characterize the pharmacokinetic (PK) profile of the combination of MK-2206 and dinaciclib. **4**. Analyze pre-treatment tumor specimens for activation of RAS downstream pathway signaling as potential predictors of treatment benefit. **5**. Correlate post-treatment pharmacodynamic (PD) changes in tumor biopsies and peripheral blood mononuclear cells with MK-2206 and dinaciclib treatment to demonstrate proof-of-concept and assess for post-treatment predictive biomarkers.
Project Overlap or Parallel: No scientific or budgetary overlap.

AWARDED SINCE LAST SUBMISSION
None

COMPLETED SINCE LAST SUBMISSION
R21 CA172997 (PI: Azad)
Title: Targeting RAS signaling with CDK and AKT inhibition in pancreatic cancer

Time commitment: 0.6 calendar
Supporting agency: NCI
Procuring Contracting/Grants Officer: William C. Timmer,
Address of Grants Officer: 6130 Executive Blvd., Rockville, MD 20852
Performance period: 07/01/13-06/30/16
Level of funding:
Project's Goal(s): This project will encompass correlative studies for a CTEP-approved Phase I clinical trial of the CDK inhibitor Dinaciclib and the AKT inhibitor MK-2206 in pancreatic cancer. The correlative studies will include pharmacokinetic and pharmacodynamic studies, as well as mutation assessment
Specific Aims: 1: Determine the maximum tolerated dose (MTD), safety, and toxicity of the combination of MK2206 and dinaciclib in patients with advanced pancreatic adenocarcinoma; **2:** Assess the preliminary efficacy of the combination of MK2206 and dinaciclib in metastatic pancreatic cancer patients as determined by disease control rate in an expansion cohort of patients at the MTD; **3:** Characterize the pharmacokinetic (PK) profile of the combination of MK2206 and dinaciclib; **4:** Analyze pre-treatment tumor specimens for activation of Ras downstream pathway signaling as potential predictors of treatment benefit; **5:** Correlate post-treatment pharmacodynamic (PD) changes in p-ERK, p-Akt, p-S6, pRB, Ki-67, and cleaved caspase-3 in tumor biopsies and peripheral blood mononuclear cells with MK-2206 and dinaciclib exposure to demonstrate proof-of-concept and assess for post-treatment predictive biomarkers.
Project Overlap or Parallel: No scientific or budgetary overlap.

RSGM-11-084-01-TBG (PI: Nelkin)
Title: Development, Genetic Characterization and Application of New Models for MTC
Time commitment: 3 calendar
Supporting agency: American Cancer Society
Procuring Contracting/Grants Officer: Charles Saxe
Address of Grants Officer: 250 Williams St., NW, Atlanta, GA
Performance period: 01/01/2011-12/31/2015
Level of funding:
Project's Goal(s): In this project, we will develop a panel of preclinical models that closely reflect the biology of MTC. We will then characterize these MTC models extensively, and test new therapeutic approaches for MTC in this panel.
Specific Aims: 1. Development of "tumorgrafts" for MTC. **2**. Genetic characterization of MTC tumorgrafts. 3. Preclinical therapeutic development in MTC tumorgrafts
Project Overlap or Parallel: No scientific or budgetary overlap.

OTHER SUPPORT

DRAKE, CHARLES G.

ACTIVE:

W81XWH-15-1-0670 (PI: Nelkin/Drake)
Title: CDK5-A Novel Role in Prostate Cancer Immunotherapy
Time commitment: 1.92 calendar
Supporting agency: CDMRP
Procuring Contracting/Grants Officer: Kathy Robinson
Address of Grants Officer: 820 Chandler Street, Fort Detrick, MD
Performance period: 09/30/2015-09/29/2018
Level of funding:
Project's Goal(s): The goal of this project is to develop a novel, effective targeted therapeutic strategy for advanced prostate cancer, blocking several of the most common resistance mechanisms to androgen deprivation therapy (ADT), that underlie progression to castration resistant prostate cancer (CRPC)
Specific Aims: 1. Effect of dinaciclib on androgen receptor (AR) S81 phosphorylation and function. **2**. Effect of dinaciclib, alone and in combination with inhibitors of potential compensatory signaling pathways, in human prostate cancer cell lines and xenografts. **3**. Effect of dinaciclib combinations in a model of prostate cancer bone metastasis.
Project Overlap or Parallel: No scientific or budgetary overlap.

P30CA006973 (PI: Nelson/Drake)
Title: Regional Oncology Research Center (Flow Cytometry/Human Immunology Shared Resources)
Time Commitment: 1.32 calendar
Supporting Agency: National Cancer Institute
Procuring Contracting/Grants Officer: Michael Zarkin
Address of Funding Agency: 6120 Executive Blvd, Suite 243 Rockville, MD 20892
Performance Period: 05/07/1997-04/30/2017
Level of Funding:
Project's Goal: The main goal of this core is to provide state of the art flow cytometry/sorting and human immunology capability to the members of the cancer center.
Specific Aims: 1.Evaluate samples from a variety of sources
Project Overlap or Parallel: No scientific or budgetary overlap

R01CA154555 (PI: Drake)
Title: Role of Tc17 cells in tumor immunotherapy
Time commitment: 2.28 calendar
Supporting Agency: National Cancer Institute
Procuring Contracting/Grants Officer: Connie Murphy
Address of Funding Agency: 6120 Executive Blvd, EPS/Suite 243, Rockville, Md. 20892-7150
Performance Period: 03/01/12- 02/28/2017
Level of Funding:
Project's Goal: These studies have broad clinical and immunological significance: successful completion of this work could transform adoptive T cell transfer for the treatment of cancer patients, and shed novel insight into fundamental aspects of CD8 function and differentiation.
Specific Aims: 1. Define the cytokine and cellular requirements for Tc17 mediated immunotherapy in vivo 2. Understand the TCR/peptide and peptide/MHC interactions critical for Tc17 skewing in vitro. 3. Establish the requirements for Tc17 conversion to an IFN-γ secreting phenotype 4. Determine the molecular mechanisms underlying Tc17 persistence in vivo.
Project Overlap or Parallel: No scientific or budgetary overlap

CA224-020 (PI: Drake)
Title: A Phase 1 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability, and Efficacy of Anti-LAG-3 Monoclonal Antibody (BMS-986016) Administered Alone and in Combination with Anti-PD-1 Monoclonal Antibody (Nivolumab, BMS-936558) in Advanced Solid Tumors
Time commitment: .12 calendar
Supporting Agency: Bristol Myers Squibb Co
Procuring Contracting/Grants Officer: Dan Fontana
Address of Funding Agency: Route 206 & Province Line Road, Princeton, NJ 08543
Performance Period: 11/12/2013-11/11/2017
Level of Funding:
Project's Goal:
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

GO29313 (PI: Drake)
Title: A Phase 1, Open-Label, Dose-Escalation Study of The Safety and Pharmacokinetics of MOXR0916 Administered Intravenously As a Single Agent to Patients with Locally Advanced or Metastatic Solid Tumors
Time commitment: .12 calendar
Supporting Agency: Genentech Corporation
Name of Procuring Contracting/Grants Officer:
Address of Funding Agency: 1 DNA Way South, San Francisco, CA 94080
Performance Period: 07/07/2014-12/08/2017
Level of Funding:
Project's Goal: The major goal of this trial is to evaluate the safety and tolerability of MOXR0916 in patients with locally advanced or metastatic tumors
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

90091646 (PI: Drake)
Title: Enhancing Prostate Cancer Immunotherapy through Epigenetic Reprogramming for Optimal Activation of Specific Effector T-Cells
Time commitment: 1.2 calendar
Supporting Agency: Prostate Cancer Foundation
Procuring Contracting/Grants Officer: Howard R. Soule, PhD
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401
Performance Period: 12/24/2014-12/23/2017
Level of Funding:
Project's Goal: To evaluate the ability of a novel, multivalent cancer vaccine based on attenuated listeria monocytohenes (*Lm)* to induce prostate cancer-specific immune responses, and to attenuate tumor progression.
Specific Aims: 1. Evaluate a novel, trivalent prostate cancer vaccine based on an attenuated listeria platform for safety, tolerability and preliminary evidence of efficacy in men with metastatic castration-resistant prostate cancer (mCRPC). 2. Determine the magnitude and breadth of antigen-specific T and B cell immune responses induced by this novel vaccine. 3. Using biopsies of metastatic lesions, quantify the induction of a pro-inflammatory immune infiltrate as well as expression of checkpoint ligands (including PD-L1) for potential utility as predictors of response and/or resistance.
Project Overlap or Parallel: No scientific or budgetary overlap

90054364 (PI: Pardoll/Drake)
Title: International Immuno-Oncology Network-IION Resource Model
Time commitment: .12 calendar
Supporting Agency: Bristol-Myers Squibb Co

Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 & Province Line Road, Princeton, NJ 08543
Performance Period: 05/07/2013-05/06/2017
Level of Funding:
Project's Goal: The major goal of this clinical research network is to conduct immunotherapy trials with novel agents including anti-KIR, anti-CD137 and others, and to collaboratively evaluate pharmacodynamics and potential biomarkers of response.
Specific Aims: 1. Analyze immune-inhibitory networks in resected tumors employing 3 techniques for geographic localization: (i) IHC, (ii) amplified ISH, and (iii) qRT-PCR analysis of laser capture micro-dissected (LCM) regions of leukocytic infiltration. 2. Complementary to the studies in 1, we will sort myeloid, lymphoid and cancer cells from freshly dissociated tumors in cases where enough tumor is available, allowing analysis by flow cytometry and mRNA profiling of cellular subsets for co-expression of inhibitory ligands, receptors and druggable metabolic enzymes.
Project Overlap or Parallel: No scientific or budgetary overlap

COMPLETED SINCE LAST SUBMISSION

W81XWH-12-1-0170 (PI: Platz/Drake)
Title: Prospective Evaluation of Intraprostatic Inflammation and Focal Atrophy as a Predictor of Risk of High-Grade Prostate Cancer and Recurrence after Prostatectomy
Time commitment: .6 calendar
Supporting Agency: US Department of Defense
Procuring Contracting/Grants Officer: Kathy E. Robinson.
Address of Funding Agency: 1077 Patchel Street, Fort Detrick, MD 21702-5024
Performance Period: 07/01/2012-06/30/2015
Level of Funding:
Project's Goal: To evaluate several possible predictors of high-grade prostate cancer in men who have undergone a prostatectomy.
Specific Aims: We propose to evaluate the following with respect to risk high-grade prostate cancer: 1. The association of a. extent of inflammatory infiltrates, and b. type of immune cells present in benign prostate tissue with subsequent risk of prostate cancer, especially high-grade disease. 2. The association of a. extent and morphologic type of focal atrophy, and b. biological characteristics in benign prostate tissue with subsequent risk of prostate cancer, especially high-grade disease. With respect to risk of prostate cancer recurrence, we propose to evaluate the following: 3. The association of a. extent of inflammatory infiltrates, and b. type of immune cells present in benign and malignant prostate tissue with subsequent risk of prostate cancer recurrence. 4. To evaluate the association of a. extent and morphologic type of focal atrophy, and b. biological characteristics in benign prostate tissue and near cancer with subsequent risk of prostate cancer recurrence.
Project Overlap or Parallel: No scientific or budgetary overlap

W81XWH-13-1-0369 (PI: Drake)
Title: Immunological Targeting of Tumor-Initiating Prostate Cancer Cells
Time commitment: 1.2 calendar
Supporting Agency: US Congressionally Directed Medical Research
Procuring Contracting/Grants Officer: Josh McKean
Address of Funding Agency: 820 Chandler Street, Ft. Detrick, MD 21702
Performance Period: 09/30/2013-09/29/2016
Level of Funding:
Project's Goal: Our goal in these studies is to eliminate castrate-resistant, luminal epithelial cells (CRLEC) using the immune system.
Specific Aims: 1. Identify and verify antigenic targets specifically associated with Castrate Resistant Luminal Epithelial Cells (CRLEC's). 2. Using a novel vaccine platform based on cyclic di-nucleotides (CDN) as an adjuvant, rapidly screen a panel of promising CRLEC targets in intact and castrate animals.

Project Overlap or Parallel: No scientific or budgetary overlap

274053 (PI: Drake)
Title: Next Generation Vaccines to Augment Anti-PD-1 Immunotherapy for Melanoma (Academic-Industry Partnerships Award)
Time commitment: .24 calendar
Supporting Agency: Aduro Biotech (Industry portion)
Procuring Contracting/Grants Officer: Stephen Isaacs
Address of Funding Agency: 626 Bancroft Way, Berkeley, CA 94710-2224
Performance Period: 07/01/2013-06/30/2016
Level of Funding:
Project's Goal: The major goal of this project is to optimize a vaccine/anti-PD-1 combination regimen, aiming for rapid clinical translation.
Specific Aims: 1. Test the hypothesis that an anti-melanoma vaccine based on attenuated listeria monocytogenes (LM) can enhance significant CD8 infiltration in established melanomas, and synergize with PD-1 blockade to mediate tumor regression. 2. Test the hypothesis that an anti-melanoma vaccine combining cyclic di-nucleotides (CDN) with melanoma-specific peptide antigens will demonstrate preclinical anti-tumor efficacy in combination with PD-1 blockade. 3. Determine whether heterologous prime / boost vaccination, sequencing CDN-based and/or LM-based vaccination with conventional vaccines (cell based, viral, peptide) shows additive or synergistic effects in preclinical melanoma models.
Project Overlap or Parallel: No scientific or budgetary overlap

SU2C-AACR-DT10 (PI: Pardoll/Drake)
Title: Immune Checkpoint Blockade and Adoptive Cell Transfer in Cancer Therapy
Time commitment: .24 calendar
Supporting Agency: University of Texas M.D. Anderson Cancer Center (AACR Prime)
Procuring Contracting/Grants Officer: Renee Gonzales
Address of Funding Agency: 1515 Holcombe Blvd, Houston, Texas 77030
Performance Period: 03/01/2013-02/28/2016
Level of Funding:
Project's Goal: The major goal of this project is to enable the rapid and rational clinical investigation of new discoveries in one of the most promising areas of oncology research today, immune checkpoint blockade. **Specific Aims:** 1. Interrogation of immune responses within the tumor microenvironment before and after treatment with immune checkpoint blockade 2. Interrogation of the targets of T and B cell responses after checkpoint blockade 3. Development of combinatorial cancer therapies based on checkpoint blockade.
Project Overlap or Parallel: No scientific or budgetary overlap

90055855 (PI: Drake)
Title: Comprehensive Transcriptional Profiling of Human Prostate-cancer infiltrating cells
Time commitment: .12 calendar
Supporting Agency: Janssen Research and Development LLC
Procuring Contracting/Grants Officer: Joseph Erhardt
Address of Funding Agency: 920 Route 202 South, Raritan, NJ, 08869
Performance Period: 09/09/2013-09/08/2015
Level of Funding:
Project's Goal: The major goals of this project are to establish a specific immunologic profile of prostate cancer and identify new potential immunological targets to combat T-cell exhaustion and ultimately improve outcomes for patients with prostate cancer by allowing for discovery of specific immunologic therapies for prostate cancer that will create a durable immune response
Specific Aims: 1. Create an immunologic profile unique to prostate infiltrating lymphocytes as compared to matched peripheral blood lymphocytes by comparing naïve activated T-cells to determine

which receptors are associated with exhaustion versus activation in CD4+ and CD8+ lymphocytes. 2. Evaluate immunologic phenotype of surrounding epithelial cells of the tumor microenvironment as compared with that of adjacent normal tissue to identify potential molecular tumor targets as well as co-inhibitory immunological receptors
Project Overlap or Parallel: No scientific or budgetary overlap

MDX1106-03 (PI: Brahmer/Drake)
Title: A Phase 1B, Open-Label, Multicenter Multidose, Dose-escalation Study of MDX-1106 in subjects with selected advanced or recurrent malignancies
Time commitment: .12 calendar
Supporting Agency: Medarex, Inc
Procuring Contracting/Grants Officer: Christina S. Schade
Address of Funding Agency: 519 Route 173 West Broomsbury, NJ 08804
Performance Period: 04/13/2009-11/30/2015
Level of Funding:
Project's Goal: The overall objective of this proposal this is a Phase I clinical trial of the novel, fully human anti-PD-1 monoclonal antibody in patients with advanced cancer.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

CA184-095-181 (PI: Drake)
Title: Randomized, Double-Blind, Phase 3 Trial to Compare the Efficacy of Ipilimumab vs Placebo in Asymptomatic or Minimally Symptomatic Patients with Metastatic Chemotherapy-Naive CRPC
Time commitment: .12 calendar
Supporting Agency: Bristol-Myers Squibb Co
Procuring Contracting/Grants Officer: Mahrukh Mobed
Address of Funding Agency: Route 206 & Province Line Road, Princeton, NJ 08543
Performance Period: 08/11/2011-07/31/2015
Level of Funding:
Project's Goal: The primary objective of this clinical trial is to compare overall survival of subjects with chemotherapy-naïve castration resistant prostate cancer who have been randomized to Ipilimumab vs. placebo.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

CA184-043-159 (PI: Drake)
Title: Randomized, Double-Blind, Phase 3 Trial Comparing Ipilimumab vs. Placebo Following Radiotherapy in Subjects with Castration Resistant Prostate Cancer that Have Received Prior Treatment with Docetaxel
Time commitment: .12 calendar
Supporting Agency: Bristol-Myers Squibb Co
Procuring Contracting/Grants Officer: William Candela
Address of Funding Agency: 5 Research Parkway, 2AW-321, Wallingford, CT 06492
Performance Period: 12/1/2009-11/30/2014
Level of Funding:
Project's Goal: The primary objective of this clinical trial is to compare overall survival of subjects with castration resistance prostate cancer and previously treated with Docetaxel who have been randomized to Ipilimumab vs placebo
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

CA209-009 (PI: Drake)

Title: An Exploratory Study to Investigate the Immunomodulatory Activity of Various Dose Levels of Anti Programmed-Death-1 Antibody (BMS-936558) in Subjects with Metastatic Clear Cell Renal Cell Carcinoma
Time commitment: .12 calendar
Supporting Agency: Bristol-Myers Squibb Co
Procuring Contracting/Grants Officer: Dan McDonald
Address of Funding Agency: Route 206 & Province Line Road, Princeton, NJ 08543
Performance Period: 10/01/11-09/30/2015
Level of Funding:
Project's Goal: The primary objective is to investigate the Pharmacodynamic Immunomodulatory activity of Anti-PD-1 Antibody (BMS-936558) on circulating T cell subsets (activated and memory T cells), serum chemokines (CXCL9, CXCL10) and on CD4 and CD8 T cell infiltrations in tumors in subjects with metastatic clear-cell RCC
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

CA220-008 (PI: Drake)
Title: A Phase 1 Dose Escalation Study of BMS 982470 (Recombinant Interleukin-21, rIL-21) in combination with BMS 936558 (Anti-PD-1) in Subjects with Advanced or Metastatic Solid Tumors
Time commitment: .12 calendar
Supporting Agency: Bristol-Myers Squibb Co
Procuring Contracting/Grants Officer: Donna Morgan Murray
Address of Funding Agency: 345 Park Avenue, New York, NY 10154
Performance Period: 09/01/2012-08/31/2015
Level of Funding:
Project's Goal: The goal of this study is to demonstrate adequate safety and tolerability of the combination therapy so as to permit further testing and studies.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

SMRH-200775534.4 (PI: Drake)
Title: LM based vaccines and Cyclic DiNucleotides (CDN) in Anti-tumor immunity
Time commitment: 1.2 calendar
Supporting Agency: Aduro Biotech
Procuring Contracting/Grants Officer: Stephen T. Isaacs
Address of Funding Agency: 626 Bancroft Way, Berkeley, CA 94710-2224
Performance Period: 08/14/2014-08/13/2016
Level of Funding:
Project's Goal: The major goal of this project is to drive alternative combination immunotherapy regimens, such as combining CDN with epigenetic modifying agents like 5-azacytadine and/or HDAC inhibitors, both of which are currently being evaluated in Phase 1 trials in the JHU cancer center
Specific Aims: 1. To determine the LM-based molecule(s) that prevent PD-1 up-regulation 2. Optimizing LM-based vaccines as a priming vector by manipulation of IFN-β secretion 3. Identification of antigens targeted by curative IntraTumoral (IT) treatment with cyclic dinucleotides (CDN)
Project Overlap or Parallel: No scientific or budgetary overlap

P30AI094189 (PI: Chaisson/Drake)
Title: The Johns Hopkins Center for AIDS Research(Supplement: Combined Immune Checkpoint Blockade to Enhance NK Cell and CD8+ T Cell Targeting of HIV-1 Reservoirs)
Time commitment: .12 calendar
Supporting Agency: National Institute of Allergy and Infectious Diseases
Procuring Contracting/Grants Officer: Ann Namking Lee

Address of Funding Agency: 6700-B Rockledge Drive, Rm 4211, Bethesda, MD 20892-7620
Performance Period: 08/01/2014-07/31/2015
Level of Funding:
Project's Goal: The goal of this supplemental project is to determine whether it's possible to improve the immune response to HIV infection by blocking the normal negative feedback response of the immune system. To do this we will use a mouse model of HIV infection and will treat the mice with immune enhancers that have been successful in treating some forms of cancer
Specific Aims: 1. To determine whether a single or combined immune checkpoint blockade can lead to a functional cure in a clinically relevant model of HIV based on immunodeficient mice reconstituted with PBMC from HIV patients on suppressive HARRT regimens. 2. To determine whether combining a potent dendritic-cell (DC) vaccine with immune checkpoint blockade can lead to a functional cure in a clinically and physiologically relevant model of HIV introduced in Aim 1.
Project Overlap or Parallel: No scientific or budgetary overlap

(PI: Drake)
Title: Understanding Checkpoint Expression and Function in GBM RCC and Bladder CA by Integrated Analysis of Tumor Infiltrating Lymphocytes and Tumor Cells
Time commitment: .12 calendar
Supporting Agency: Bristol-Myers Squibb Co
Procuring Contracting/Grants Officer: Les Enterline
Address of Funding Agency: Route 206 & Province Lane Road, Princeton, NJ 08543
Performance Period: 10/1/2014-06/30/2015
Level of Funding:
Project's Goal: The major goals of this project is to determine the relative expression of known and novel checkpoint molecules in pathologist-curated patient samples and the functional significance of these molecules using micro-scale functional assays.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

90091646 (PI: Drake)
Title: Enhancing Prostate Cancer Immunotherapy through Epigenetic Reprogramming for Optimal Activation of Specific Effector T-Cells
Time commitment: 1.2 calendar
Supporting Agency: Prostate Cancer Foundation
Procuring Contracting/Grants Officer: Howard R. Soule, PhD
Address of Funding Agency: 1250 Fourth Street, Santa Monica, CA 90401
Performance Period: 12/24/2014-12/23/2017
Level of Funding:
Project's Goal: To evaluate the ability of a novel, multivalent cancer vaccine based on attenuated listeria monocytohenes (*Lm)* to induce prostate cancer-specific immune responses, and to attenuate tumor progression. **Specific Aims:** 1. Evaluate a novel, trivalent prostate cancer vaccine based on an attenuated listeria platform for safety, tolerability and preliminary evidence of efficacy in men with metastatic castration-resistant prostate cancer (mCRPC). 2. Determine the magnitude and breadth of antigen-specific T and B cell immune responses induced by this novel vaccine. 3. Using biopsies of metastatic lesions, quantify the induction of a pro-inflammatory immune infiltrate as well as expression of checkpoint ligands (including PD-L1) for potential utility as predictors of response and/or resistance.
Project Overlap or Parallel: No scientific or budgetary overlap

15003789 (PI: Paller/Drake)
Title: Overcoming drug resistance in metastatic castration resistant prostate cancer Activation of Specific
Time commitment: .6 calendar
Supporting Agency: The Community Foundation for the National Capital Region

Procuring Contracting/Grants Officer: K. Matthews
Address of Funding Agency: 1201 15th St, NW, suite 420, Washington, DC 20005
Performance Period: 11/14/2014-11/13/2016
Level of Funding:
Project's Goal: The goal of this clinical trial is to evaluate a new combination therapy to extend the life of men with advanced prostate cancer.
Specific Aims: N/A
Project Overlap or Parallel: No scientific or budgetary overlap

AWARDED SINCE LAST SUBMISSION
None

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS
Nothing to Report

9. APPENDICES:
None